

URIDINE TOXICITY

Reports on the toxicity of Uridine in literature are uncommon, both because the compound is very safe, and because it has been introduced in therapy in Italy more than 30 years ago, when requirements for toxicity by regulatory bodies were not very stringent. Here we summarize the available reports and their sources:

1. Animal data published in russian:

"Acute and chronic toxicity of uridine and inosine" by I.Petersone, S.Germane, D.Berzina, U.Mikstais (from Inst.Org.Sint., Riga, URSS). Eksp.Klin.Farmakoter. 1987, 16, 134-7: Acute toxicity studies in both mice and rats showed oral LD50 values for uridine and inosine to be > 10 g/Kg. I.v. LD50 values of both compounds were >0.5 g/Kg in both species, and i.p. toxicities were even lower. Chronic toxicity studies of uridine and inosine in dogs and rats also revealed very low toxicity.

2. Animal data recovered from Polifarma files:

Polifarma performed a complete set of pharmaco-toxicological studies on Uridine and a mixture containing also Cytidine and Glutamine in 1968, prior to clinical studies on the product "Centrum". The complete report (in italian) is still available.

From that report, and from other toxicity studies performed in more recent times (whose reports are available only as summary tables), it is possible to conclude that the LD50 of uridine is over 2 g/Kg by injection (both i.p. and i.v.) in mice and rats, and over 4 g/Kg in both species by oral route.

As regards chronic administration in rats (100 mg/Kg by oral route, and 50 mg/Kg i.p., for 180 days), no differences with controls were observed for all the considered parameters.

Similarly, no toxicity signs were detected in rats, treated with oral doses between 166 and 500 mg/Kg/day for 30 days; in rabbits orally treated with 104 or 208 mg/Kg/day for 30 days; in rats treated by oral route with 83 to 250 mg/Kg/day for 120 days; in dogs orally treated with 104 to 250 mg/Kg/day for 120 days.

Uridine had no toxic effects on fertility, embriogenesis and peri-post natal complicances in rats and rabbits at oral doses between 50 and 416 mg/Kg/day.

Finally, no toxic effects were found on blood pressure, breath, and ECG of rats, rabbits and cats treated orally or by injection up to 200 mg/Kg.

3. Human studies:

Because of the pharmacological use of high doses of Uridine in the rescue therapy after administration of the anticancer drug 5-FU, several safety studies have been performed and published, describing the use of Uridine in healthy volunteers or in cancer patients.

For example, in Cancer Research (44, 5928-33, 1984) A.Leyva and coll. reported that "Uridine was administered at 1 hour i.v. infusion at doses of 1 to 12 g/sq m. ...In 23 courses of uridine alone, the only toxicity observed was transient shivering after one of two courses at 12 g/sq m. This side effect was also seen after administration of uridine (10 g/sq m) during combination with 5-FU". In Cancer Treat Rep (70, 745-50, 1986), C.J. van Groeningen and coll. referred that "Uridine administration was examined as a continuous infusion at 1 and 2.5 g/m²/hr (two patients) and as a series of intermittent infusions during 72 hours at doses of 1-3 g/m²/hr, whereby 3-hr uridine administration was alternated with 3-hr treatment-free interval (six patients). Continuous infusion of uridine was discontinued due to rapid increase in body temperature". It was later demonstrated (Pharmaceutical Res. 4, 113-9, 1987) that fever is due to accumulation of β -alanine, a metabolite of uracil. In J.Natl.Cancer Inst. (83, 437-41, 1991), C.J. van Groeningen and coll. studied the effects of orally administered Uridine in six healthy volunteers and nine patients with metastatic colorectal cancer: "Oral Uridine was studied as single-dose administrations at doses escalating from 0.3 to 12 g/m² and as multiple-dose administrations every 6 hours for 3 days at doses from 5 to 10 g/m². The maximum tolerated dose was 10 to 12 g/m² for a single dose of Uridine and 5 g/m² for the multiple-dose regimen. Diarrhea was the dose-limiting toxic effect.

In conclusion, therefore, the published studies suggest that Uridine is a rather safe drug in humans, at least at doses up to 10 grams: side effects over this limit appear as fever and shiverings (by i.v. injection), and as diarrhea (by oral route).

On the other hand, Uridine has been used for more than 30 years in Italy on several hundred thousand people, at doses up to 300 mg/day for several months, without reports of side effects. Moreover, small groups of children affected by Orotic aciduria are treated daily with very high doses of Uridine (200 mg/Kg) for many years, without evidence of toxic effects.

Rome, 6th march 2002

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